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Are PRP and HA Injections Beneficial for Symptomatic Relief when Administered as Combination Therapy in Patients with Knee Osteoarthritis?

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Are PRP and HA Injections Beneficial for Symptomatic Relief when Administered as Combination Therapy in Patients with Knee Osteoarthritis?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Are PRP and HA injections beneficial for symptomatic relief when administered as combination therapy in patients with knee osteoarthritis?"

STUDY DESIGN: A systematic review of two randomized control trials (RCTs) and one case series published between 2016-2018.

DATA SOURCES: Sources were found using PubMed and Cochrane. Sources were selected based on patient-oriented evidence of therapeutic effects from HA and PRP injections as monotherapy and combination therapy in symptomatic relief for patients with knee osteoarthritis.

OUTCOMES MEASURED: Patient-reported pain score was recorded after treatment using Visual Analog Scale (VAS) or Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index. One RCT used WOMAC; the other RCT and the case series used VAS.

RESULTS: One RCT (Lana JF, Weglein A, Sampson SE, et. al Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med*. 2016;12(2):69–78. Published 2016 Nov 29.) showed a significant improvement in VAS pain score when patients were treated with combination therapy vs monotherapy by HA ($p=<0.05$). Another RCT (Yu W, Xu P, Huang G, Liu L. Clinical therapy of hyaluronic acid combined with platelet-rich plasma for the treatment of knee osteoarthritis. *Exp Ther Med*. 2018;16(3):2119–2125.) showed that combination therapy also provided significant improvement ($p=<0.05$) in pain when patients reported using the WOMAC index. The case series also showed improved VAS scores before and after combination treatment (Chen SH, Kuan TS, Kao MJ, Wu WT, Chou LW. Clinical effectiveness in severe knee osteoarthritis after intra-articular platelet-rich plasma therapy in association with hyaluronic acid injection: three case reports. *Clin Interv Aging*. 2016;11:1213–1219. Published 2016 Sep 8. doi:10.2147/CIA.S114795).

CONCLUSION: The studies that were used in this systematic review conclude that combination of PRP and HA provide significantly improved results in pain when using either VAS or WOMAC indexes to assess pain before and after treatment. Future studies should consider radiographic imaging before and after treatment to produce objective results. Also, bigger sample sizes and monitoring short and long-term effects of combination therapy during trials would be beneficial since combination of HA and PRP is relatively novel.

KEYWORDS: PRP, HA, Combination, Osteoarthritis

INTRODUCTION

Knee osteoarthritis (OA) is a chronic degenerative joint disease due to loss of cartilage over time leading to joint space narrowing between the femur and tibia. The loss of cartilage and synovial fluid in the joint leads to increased bone-on-bone contact which results in decreased range of motion, inflammation, stiffness, and pain in the knee joint.[1] The significance of articular cartilage is that it acts as a buffer in order to provide flexibility and full range of motion to the knee.[2] It is composed of a dense extracellular matrix which is composed of proteoglycans, hyaluronic acid, and link protein.[2] The degenerative loss of this material in the knee joint leads to osteoarthritis. Mostly affecting the middle to elderly aged population, some risk factors of knee osteoarthritis are obesity, prior trauma to the joint, overuse of the joint, genetics, etc.[1]

Knee osteoarthritis is a common condition in the United States affecting 10% of men and 13% of women over age 60.[3] The increasing number of Americans affected with knee osteoarthritis has contributed to more than $41 billion annually in health care with an average lifetime cost being between $12,400 and $16,000 per patient.[6] In 2013, there were 20.78 million knee OA-related ambulatory visits and 2.95 million inpatient visits.[6] Due to the increasing prevalence and noncomplex initial treatment, osteoarthritis is commonly treated in primary care facilities, making it well within the scope of practice for physician assistants.[4] Initial stages of mild to moderate osteoarthritis are served with non-costly conservative treatment such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.[5] However, costs rise in treating osteoarthritis when patients fail conservative measures and/or carry multiple comorbidities. These patients eventually require invasive procedures such as intra-articular analgesia and eventual total knee replacements. In order to lower cost while providing higher

quality care by prolonging the time period before knee transplant, novel forms of treatment such as intra-articular injections of hyaluronic acid and platelet-rich plasma are being researched and gradually implemented in orthopedic practices across the country.

Current forms of treatment for arthritis such as acetaminophen, NSAIDs, and intraarticular corticosteroids provide temporary symptomatic relief by lessening joint inflammation and pain and overall improve stiffness. The gradual degeneration of the joint and cartilage is however irreversible. Conservative measures such as weight loss may decrease the pressure on joints and help delay progression of arthritis. However, understanding that knee cartilage is the foundation of the joint, research on treatment that promotes cartilage healing is being conducted.[7] Furthermore, studies have shown symptomatic relief from hyaluronic acid (HA) and platelet-rich plasma (PRP) injections.[7]

Hyaluronate occurs naturally in the joint cartilage and synovial fluid composed of *N*-acetyl-d-glucosamine and d-glucuronic acid residues.[8] When knee OA progresses and hyaluronate is depolymerized, exogenous hyaluronic acid can be injected into the joint to allow lubrication and opening of the joint.[8] On the other hand, PRP is a plasma mixture containing five times more platelets than in human blood.[9] Evidence suggests that this allows PRP to provide regenerative effects and hemostasis to the knee joint.[9] Studies exist which evaluate the effectiveness of symptomatic improvement from HA and PRP injections as monotherapy. What is unknown however, is the symptomatic benefits of combining HA and PRP in intra-articular administration.[7] Considering both products have different mechanisms of action, combination of them may produce an additive effect in providing symptomatic relief for knee OA patients.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not PRP and HA injections are beneficial in symptomatic improvement for knee osteoarthritis patients when administered as combination therapy.

METHODS

Two randomized controlled trials and one case series were used in this review. The population studied was patients with symptomatic knee osteoarthritis. The intervention in all three studies was combination of HA and PRP therapy. The comparison was HA and PRP monotherapy which was discussed in the two RCTs, not in the case series. This review will focus on effects of HA and PRP combination compared to HA monotherapy. Some tools used to report pain were Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC).[5] Using VAS to report pain makes the outcomes subjective to the patient, therefore it is patient-oriented data. Another tool to report painted oriented outcomes is WOMAC, a questionnaire asking osteoarthritis patients to report level of difficulty with daily tasks. The answers on the WOMAC questionnaire help data collectors to develop a total score between 0-20 for pain, 0-8 for stiffness, and 0-68 for functional disability.[2] The RCT by Lana et. al and case series by Chen et. al used VAS to report knee pain in patients. However the RCT by Yu et. al used the WOMAC index to report pain.

All studies in this review are in English, were published in peer-reviewed journals, and found on PubMed and Cochrane libraries. Keywords used to find them were “PRP”, “HA”, “combination”, and “osteoarthritis.” The inclusion criteria for this review were subjects with symptomatic knee osteoarthritis. In addition RCTs, case reports, or case series published in the past 5 years were included. Studies excluded were ones older than 5 years and ones that did not

report patient-oriented outcomes. The data reported in these studies includes mean changes and p-values.

Table 1- Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Lana[5] (2016)	Double Blind RCT	105	45-69 years (mean age: 60.9 years)	-age 40-70 -mild to moderate OA with radiographic evidence -chronic pain for at least 4 mo. And/or joint edema	-coagulopathies -axial deviation of lower limb> 5o for valgus and varus knee -severe CVD, DM, immunosuppressed pt -on anti-coagulants, antithrombotic, and anti-platelet	15	Intra-articular injections of PRP and HA as combination therapy
Yu[7] (2018)	Double Blind RCT	360	22-72 years	-Karnofsky performance status >80% (difficulty walking by themselves and have knee pain)	-Pts with DM, immunodeficiency, malignancy. -on anti-coagulants, antithrombotic, and anti-platelet -NSAIDs 2 days before injection -Hgb<12 -Plt ct<150,000 -valgum/varum>20o -egg/avian protein allergy	83	Intra-articular injections of PRP and HA as combination therapy
Chen[2] (2016)	Case Series	3	69-77 Years (pt 1: 69 pt 2: 76 pt 3: 77)	Symptomatic mild to moderate knee OA	*Not specified*	0	Intra-articular injections of PRP and HA as combination therapy

OUTCOMES MEASURED

All studies evaluated symptomatic improvement after monotherapy of HA or PRP combination therapy. In the Lana et. al study, changes in pain level were reported by patients using VAS.[5] The HA group received 2.0 mL of high molecular weight non cross-linked hyaluronic acid extracted from bacterial cells. The combination received 2.0 mL of HA followed by 5 mL of PRP. After administration all patients applied ice-packs for 30 minutes, three times a day, for 2 days after injection. Patients were screened at baseline and then monitored for one year at four intervals: 1 month, 3 months, 6 months, and 1 year.[5] The median change in VAS scores in 1 year was analyzed in this review.[5]

The Yu et. Al study used the WOMAC scale for patient-reported pain, stiffness, and functional limitation changes after treatment.[7] A total of 360 patients were divided into groups where they received weekly double-blind treatment with HA, PRP, combination of PRP and HA, or a placebo.[7] The HA group received weekly administration of 0.20 mg of HA and the PRP group received weekly administration of 8 mL of PRP for 8 weeks. The WOMAC pain, stiffness, and physical function was reported at baseline and at the 52 week post-treatment mark. A change in score was analyzed and p-values to assess significance were generated.[7]

The case series by Chen et. Al included three cases of moderate to severe osteoarthritis patients where VAS was used to report pain before and after one treatment of combination HA and PRP therapy. Each patient was injected with 10 mL of PRP.[2] Two types of HA was used: two of the patients were injected with 20 mg/2mL of Hyalgan and the other was injected with 10mg/mL of Ostenil.[2]

RESULTS

All studies examined the effects of combination HA and PRP therapy on osteoarthritis patients. The two RCTs compared effects of combination therapy vs effects of monotherapy. The case series monitored effects of combination PRP and HA therapy with no comparison to monotherapy. The Lana et. al RCT included 105 patients who were all overweight per BMI and had moderate knee osteoarthritis.[5] Majority of the patients had comorbidities such as hypothyroidism, dyslipidemia, and hypertension.[5] Patients were divided into 3 groups where they received either HA (n=36), PRP, (n=36) or HA+PRP therapy (n=33). Patients were assessed at baseline, one month, 3 months, 6 months, and 1 year.[5] Pain reduction was statistically significant in the combination group at all time intervals. Data is shown in table 2.

Table 2: Lana et. al Mean change in VAS pain score at Baseline and Days Post-treatment[5]

	Mean Change in HA	Mean change in HA+PRP	P-values HA vs HA+PRP
Baseline	7.0	7.0	0.1447
30 days	-3.0	-4.0	0.0113
90 days	-3.0	-6.0	0.0000
180 days	-3.0	-5.0	0.0000
360 days	-2.0	-5.0	0.0000

In the Yu et. al study, 360 patients were divided into four groups to receive once weekly double-blind treatment of the following for 52 weeks: HA (n=88), PRP (n=104), combination therapy of HA and PRP (n=96), or a placebo (n=72).[7] Patients who were immunocompromised or on anti-coagulants were excluded from the study.[7] Pain was assessed using the WOMAC index at baseline and at 52 weeks.[7] The study concluded that combination of PRP and HA treatment showed improved WOMAC pain score vs HA or PRP monotherapy.[7] Data for this is shown in table 3.

Table 3: Yu et. al Mean change in WOMAC pain score at Baseline and Days Post-treatment[7]

	Mean Pain Score in HA Group	Mean Pain Score in HA+PRP Group
Baseline	8.91	8.94
52 weeks	5.26	3.32
Mean Change	3.61	5.58
P-Value	0.01	<0.0001

In the Chen et. al case series, 3 patients were evaluated at the China Medical University Hospital in 2014.[2] Case 1 and case 2 were given weekly PRP+HA combination therapy for 6 weeks and asked to report pain using VAS before and after treatment.[2] Case 3 was given combination therapy weekly for a total of 3 weeks and an additional treatment after five months due to continued pain. The patients in the study included case 1: a 77-year old female with normal BMI and no previous knee trauma who received weekly combination HA and PRP therapy for 6 weeks, case 2: a 69-year old overweight female who regularly visited physical therapy for gait disturbance and received weekly combination therapy for 6 weeks, and case 3: a 76-year old female who also regularly sees physical therapy for gait disturbance who received weekly combination therapy for 3 weeks.[2] Patient case 1 reported an 85 on VAS pain score (0-100) before treatment and 23 after 6 weeks of treatment, Patient 2 reported 87 before treatment and 30 after treatment. Patient 3 reported 81 before treatment and 0 after treatment.[2] A mean change or p-value was not calculated in this study.

DISCUSSION

Osteoarthritis is a progressive disease resulting in joint cartilage loss, synovitis, and subchondral bone remodeling which results in pain and loss of function.[2] Long-term treatment of knee osteoarthritis is challenging with the goal being to prolong conservative treatment until knee replacement is absolutely necessary. With the short life of oral or intraarticular analgesics,

intraarticular hyaluronic acid and platelet-rich plasma injections have been considered to prolong the time before knee replacement.[2] PRP is considered a multifunctional platelet concentrate that promotes synovial cell proliferation and cartilage recovery.[7] This is a beneficial treatment because unlike NSAIDs, PRP therapy attempts to reverse the degenerative processes faced in knee osteoarthritis.[7] On the other hand, HA therapy has more viscoelastic and lubricant properties of the synovial fluid in the knee joint. Injection of this mimics the effects of synovial fluid and improves pain and function.[7]

The idea that the combination of both of these products could produce an additive effect on symptomatic relief in knee osteoarthritis is a relatively novel topic that has been researched in very few studies. This review analyzed two RCTS and one case series in order to assess the efficacy of combination PRP and HA injections. The Lana et. al RCT showed significant improvement in VAS pain scores in patients receiving combination therapy vs HA monotherapy at all intervals assessed.[5] According to literature, because of the difference in mechanism of action of both PRP and HA, it demonstrates better effects in pain improvement.[5] The time the combination of HA and PRP takes to create an effect on patients is about 30-90 days, which explains the greatest change in pain scores between that time.[5] One limitation to consider however in this RCT is that more patients in the combination treatment group had comorbidities such as hypothyroidism and hypertension compared to other groups. Another limitation of this study was the absence of imaging to assess the efficacy of combination treatment objectively.[5] MRI would have helped identify improvement in osteoarthritic changes however this was not feasible due to cost.[5]

The Yu et. al study demonstrated that combination therapy resulted in statistically significant improvement in pain however, HA monotherapy produced statistically significant

results as well in improvement of WOMAC pain scores.[7] Some treatment-adverse effects mentioned from HA therapy alone were hypertension and proteinuria.[7] An important factor to note however, is that out of 360 patients, 25% stopped participation and could not finish all phases of treatment due to side effects such as hypertension, constipation, or diarrhea.[7] Overall, this study concluded that combination of HA and PRP therapy is beneficial in long-term pain improvement and additional trials should be conducted.[7]

The Chen et. al case series reported the three osteoarthritis patients having pain improvement as well as better physical function post combination therapy.[2] It also confirmed efficacy of combination treatment with knee x-rays before and after treatment which showed regeneration of articular cartilage.[2] There were quite a few limitations in this study. First, this was a case series only containing 3 patient cases. A larger patient population would have provided stronger data. In addition, this case series only tested combination therapy of HA and PRP.[2] There was no control group. In addition, knee X-rays were not all performed standing.[2] Uniformity of having all patients standing would have possibly allowed better measurement of articular changes before and after treatment.[2] The authors of this study concluded that further studies in a randomized setting with a larger patient population and a control groups is necessary.[2]

CONCLUSION

The studies examined in this systematic review provide favorable data for efficacy of combination treatment of HA and PRP vs HA monotherapy. The Lana et. al RCT showed significantly improved pain from combination therapy vs HA therapy alone up to one year after treatment.[5] In addition, the Yu et. al RCT also concluded that combination of PRP and HA was determined to be significantly more beneficial than HA monotherapy when analyzing WOMAC

pain scores.[7] Although the Chen et. al case series also supported the conclusion that combination therapy significantly provided pain relief, it did not have a control group to compare treatment effects with. In addition, the case series only included three cases. If there were more patients included in the study it would have strengthened the data.

Further studies should be done that include larger patient population in order to provide more accurate data. In addition, further RCTs should consider investigating the effects of PRP and HA combination treatment by evaluating radiographic imaging before and after treatment in order to make objective conclusions. Also, since combination PRP and HA therapy is relatively novel, future trials should also consider monitoring patient safety and note common short-term and long-term treatment-adverse events.

REFERENCES

1. Sun X, Zhen Z, Hu X, et al. Osteoarthritis in the middle-aged and elderly in China: prevalence and influencing factors. *International Journal of Environmental Research and Public Health.* 2019;16(23):1-18. doi: 10.3390/ijerph16234701

2. Chen SH, Kuan TS, Kao MJ, Wu WT, Chou LW. Clinical effectiveness in severe knee osteoarthritis after intra-articular platelet-rich plasma therapy in association with hyaluronic acid injection: Three case reports. *Clin Interv Aging*. 2016;11:1213–1219. Published 2016 Sep 8. doi:10.2147/CIA.S114795

3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis [published correction appears in Clin Geriatr Med. 2013 May;29(2):ix]. *Clin Geriatr Med*. 2010;26(3):355–369. doi:10.1016/j.cger.2010.03.001

4. Evaniew AL, Evaniew N. Knee osteoarthritis: Therapeutic alternatives in primary care. *World J Orthop*. 2017;8(2):187–191. Published 2017 Feb 18. doi:10.5312/wjo.v8.i2.187

5. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med*. 2016;12(2):69–78.

6. Ong KL, Runa M, Lau E, Altman RD. Cost-of-illness of knee osteoarthritis: Potential cost savings by not undergoing arthroplasty within the first 2 years. *Clinicoecon Outcomes Res*. 2019;11:245–255. Published 2019 Mar 14. doi:10.2147/CEOR.S170119

7. Yu W, Xu P, Huang G, Liu L. Clinical therapy of hyaluronic acid combined with platelet-rich plasma for the treatment of knee osteoarthritis. *Exp Ther Med.* 2018;16(3):2119–2125

8. Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. *Clin Transl Med*. 2018;7(1):6. Published 2018 Feb 16. doi:10.1186/s40169-017-0180-3

9. Glynn LG, Mustafa A, Casey M, et. al Platelet-rich plasma (PRP) therapy for knee arthritis: A feasibility study in primary care. *Pilot Feasibility Stud*. 2018;4:93. Published 2018 Jul 4. doi:10.1186/s40